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Individual Variation in Human Percutaneous Absorption and the Correlation of Percutaneous Absorption and Transepidermal Water Loss (TEWL)

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Introduction

The skin is recognized both as a barrier to percutaneous absorption and as a primary route to the systemic circulation. The skin's barrier properties are often, but not always, impressive. Fluids and electrolytes are reasonably well retained within the body, while at the same time many foreign chemicals are partially restricted from entering the systemic circulation. Despite these barrier properties, the skin is the route by which many chemicals enter the body. In most instances the toxicology of the chemical is slight, and/or the bioavailability (rate and amount of absorption) of the chemical is too low to cause an immediate response. However, some chemicals applied to the skin have the potential to produce toxicity.

Percutaneous absorption is defined as the rate and extent that a chemical is absorbed into and through the skin and into the systemic circulation. We are a world of individuals, and percutaneous absorption will vary by individual, as well as anatomic site. Where percutaneous absorption is the passage of chemicals from the outside environment into and through skin, transepidermal water loss (TEWL) is the passage of water in the other direction, from the body through the skin into the outside environment. Rates of TEWL have been shown in some, though not all, studies to correlate with rates of percutaneous absorption. Inter-individual variation in TEWL thus confirms the observed inter-individual variation in percutaneous absorption.

Individual Variation

It is well understood that chemical trials are designed with multiple volunteers to account for individual subject variation. This extends to in vivo percutaneous absorption where individual subject variability has been demonstrated.[1] This subject variation also extends to in vitro human skin samples.[2] Table 1 shows the in vitro percutaneous absorption of vitamin E acetate through human skin in vitro. Percent doses absorbed for two formulations, A and B, are shown for 24-h receptor fluid accumulation and for skin content (skin digested and assayed at 24-h time point). Assay of skin surface soap and water wash at the end of the 24-h period gives dose accountability.

The two formulations were the same except for slight variation in pH. Statistically, there was no difference in absorption between the two formulations. However, a careful examination of the individual values in Table 1 shows consistency within individuals. Analysis of variance (ANOVA) for individual variation showed statistical significance for receptor fluid ($p=.02$) and skin content ($p=.000$) (Figure 1). On the other hand, there was very clear variation among subjects. Note the consistently greater absorption in skin source 4 and the consistently greater skin content in skin source 3.

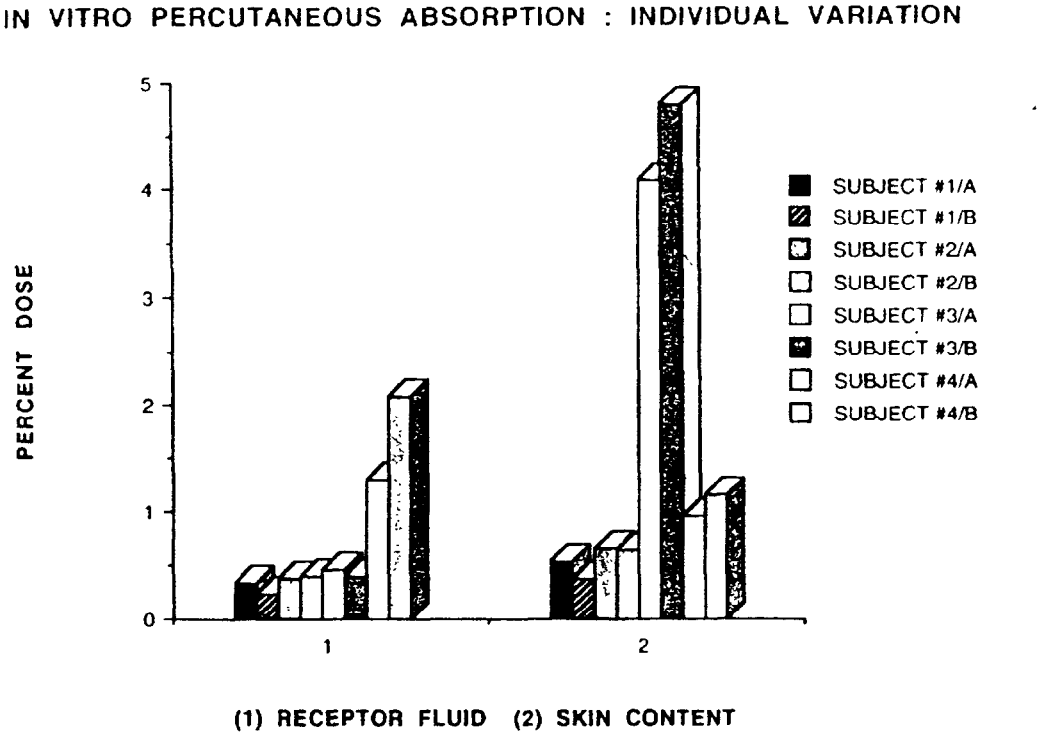
Table 1

In vitro percutaneous absorption of vitamin E acetate into and through human skin

	Percent Dose Absorbed		
	Receptor fluid	*Skin content*	*Surface wash*
Formula A:			
Skin source 1	0.34	0.55	74.9
Skin source 2	0.39	0.66	75.6
Skin source 3	0.47	4.08	89.1
Skin source 4	1.30	0.96	110.0
mean ± SD	0.63 ± 0.45[a]	1.56 ± 1.69[b]	87.4 ± 16.4
Formula B:			
Skin source 1	0.24	0.38	—
Skin source 2	0.40	0.64	107.1
Skin source 3	0.41	4.80	98.1
Skin source 4	2.09	1.16	106.2
mean ± SD	0.78 ± 0.87[a]	1.74 ± 2.06[b]	103.8 ± 5.0

[a] $P = 0.53$ (non-significant; paired t-test)
[b] $P = 0.42$ (non-significant; paired t-test)

Figure 1



Transepidermal Water Loss (TEWL)

Water comprises about 60% of adult human body weight. The body obtains water from the intake of foods and fluids, and water leaves the body visibly via urine, sweat, and feces. Additionally, the body loses water continuously by evaporation from the respiratory passages and skin surface. This loss is termed insensible water loss, because we do not feel that we are actually losing water all the time. The amount of water that is leaving the body at rest is about 700 ml/day at an ambient temperature of 20°C [3,4]. The average water loss by diffusion through the skin is 300-400 ml/day, even in a person who is born without sweat glands [4] or whose sweat glands are inactivated [5]. In other

words, the water molecules themselves actually diffuse across the skin [4]. This invisible natural process of water diffusion is called transepidermal water loss (TEWL) [3].

TEWL has been related to the skin barrier function by a series of investigations. For instance, studies in the past have established that washing the skin surface with fat solvents did not increase the rate of water loss, but light sandpapering of skin surface [6] or tape stripping of the whole stratum corneum (SC) [7,8] resulted in increased TEWL. As the permeation rate of water across full thickness skin, epidermis or SC turned out to be approximately the same, it was realized that SC acts as the principal barrier to TEWL [9]. Furthermore, a high rate of TEWL has been detected in patients with SC disorders, like psoriasis or ichthyosis [10]. TEWL is therefore taken as a measure of the skin barrier integrity which mainly resides in the SC.

Correlation of Percutaneous Absorption and TEWL

Testing of percutaneous absorption can be performed in vivo with human volunteers and animals. It can also be done in vitro with cadaver skin, human and animal, in a diffusion system. Percutaneous absorption is by passive diffusion only, from a higher concentration progressively to a lower concentration. TEWL has a passive diffusion component where water from the body (high concentration) passes out through the skin to a lower concentration, the environment. This would be baseline TEWL. TEWL also has an active component, the release of water through sweat glands for heat dissipation or nervous response. In vivo TEWL studies would measure both passive and active water transport; however, cadaver skin in *in vitro* studies would only have the passive transport.

Lotte et al. [11] studied the relationship between the percutaneous penetration of four chemicals and transepidermal water loss (TEWL) *in vivo* in man as a function of anatomic site. The findings showed an appreciable difference in the permeability of the skin from one site to another with regard to both water loss and chemical penetration. In addition, independent of the physicochemical properties of the molecules administered, there was a linear relationship between TEWL and penetration. Table 2 gives the results for the four anatomic sites (arm, abdomen, postauricular, forehead) and the four test chemicals (benzoic acid sodium salt, caffeine, benzoic acid, acetylsalicylic acid). Figure 2 illustrates the correlation between percutaneous absorption and TEWL. Correlations ranged from $r = 0.62$ to $r = 0.73$, which are good for an in vivo human study. These data confirm the utility of determination of TEWL and percutaneous absorption in the evaluation of its functional condition.

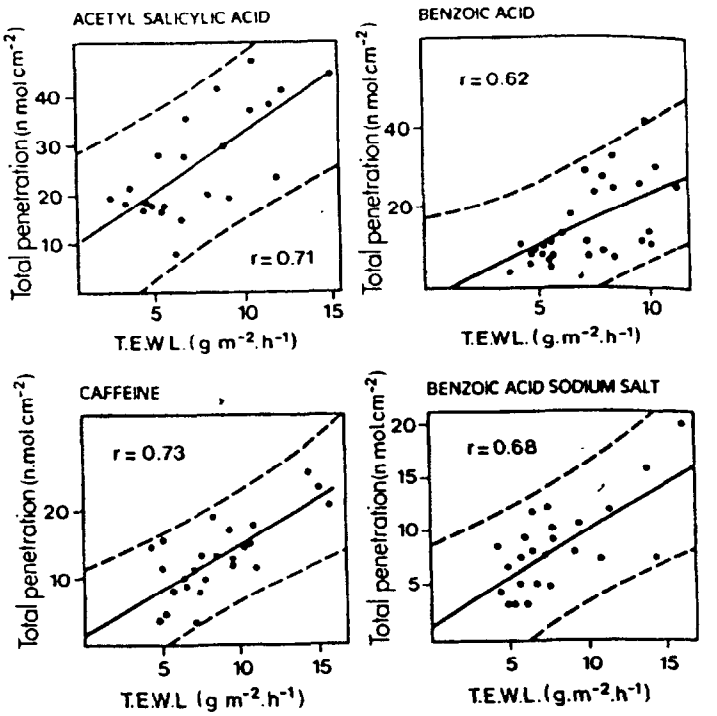
Table 2

Percutaneous absorption and transepidermal water loss (TEWL) values according to anatomic site

n	Anatomic site	Amount in urine after 24 h[a]	Total amount penetrated within 4 days[b]	Transepidermal water loss[c]	Relative permeability to arm	
					Penetration	TEWL
Compound: benzoic acid sodium salt, vehicle A						
6	Arm (upper, outer)	3 02[d] (0 34)[e]	4 02 (0 45)	6 06 (0 36)	1	1
6	Abdomen	5 73 (0 54)	7 65 (0 72)	5 37 (0 46)	1 9	0 9
6	Postauricular	7 54 (0 62)	10 06 (0 82)	7 72 (0 64)	2 5	1 3
8	Forehead	9 31 (1 76)	12 32 (2 30)	12 29 (0 96)	3 1	2
[b] Calculated from urinary excretion (b) = $\frac{(a)}{0\ 75}$						
Compound: caffeine, vehicle B						
7	Arm (upper, outer)	6 04 (0 92)	12 09 (1 84)	7 04 (0 95)	1	1
6	Abdomen	3 76 (0 67)	7 53 (1 34)	6 05 (0 43)	0 6	0 9
7	Postauricular	5 87 (0 52)	11 72 (1 05)	8 74 (0 62)	1	1 2
6	Forehead	11 17 (1 20)	22 35 (2 39)	12 77 (1 05)	1 9	1 8
[b] Calculated from urinary excretion. (b) = $\frac{(a)}{0\ 5}$						
Compound: benzoic acid, vehicle A						
8	Arm (upper, outer)	6 87 (0.75)	9 15 (1 01)	4 24 (0 35)	1	1
7	Abdomen	10 88 (1.23)	14 52 (1 64)	4 40 (0 51)	1 6	1
8	Postauricular	16 87 (3 85)	22 49 (5 14)	8 35 (0 41)	2 5	1 9
7	Forehead	20 10 (2.39)	26 80 (3 19)	10 34 (0 70)	2 9	2 4
[b] Calculated from urinary excretion: (b) = $\frac{(a)}{0\ 75}$						
Compound: acetylsalicylic acid, vehicle A						
7	Arm (upper, outer)	5 27 (0 18)	17 00 (0 37)	5 08 (0 79)	1	1
6	Abdomen	5 34 (1 03)	17 20 (3 35)	5 16 (0 43)	1	1
6	Postauricular	11 04 (2 50)	29 17 (5 37)	9 04 (0 84)	2 1	1 8
6	Forehead	10 89 (1 02)	35 14 (3 29)	11 22 (0 96)	2 1	2 2
[b] Calculated from urinary excretion: (b) = $\frac{(a)}{0\ 31}$						

[c] Measured just before the application, expressed in g m^{-2} h^{-1}
[d] Expressed in nmol cm^{-2}
[e] SD
Vehicle A (ethyleneglycol/triton X100) (90/10), Vehicle B [(ethyleneglycol/triton X100) (90/10)]/(H_2O)(50/50)

Figure 2

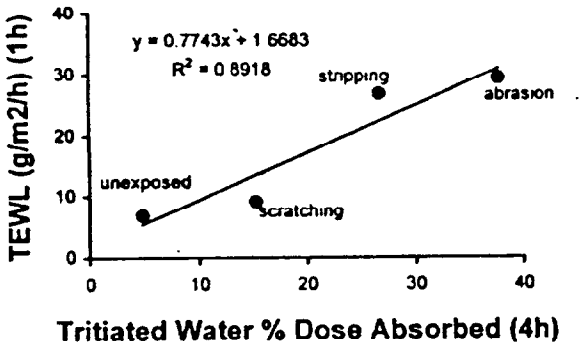


In vivo relationship between transepidermal water loss (TEWL) and percutaneous absorption of different compounds according to the anatomic site in man

Aalto-Karte and Turpeinen [12] studied in vivo percutaneous absorption of hydrocortisone in three children and six adults with widespread dermatitis after the application of 1% hydrocortisone cream. Before application of the cream, the transepidermal water loss (TEWL) was measured in six skin areas. A highly significant correlation was found between the post-application rise in plasma cortisol level and the mean transepidermal water loss. Figure 3 shows the relationship where the correlation coefficient r was a significant ($p < 0.001$) 0.991.

was no correlation between transepidermal water loss rate and $^{3}H_2O$ permeability following up to 15 tape strips ($p = 0.64$) or up to four needle-stick punctures ($p = 0.13$).

Figure 4



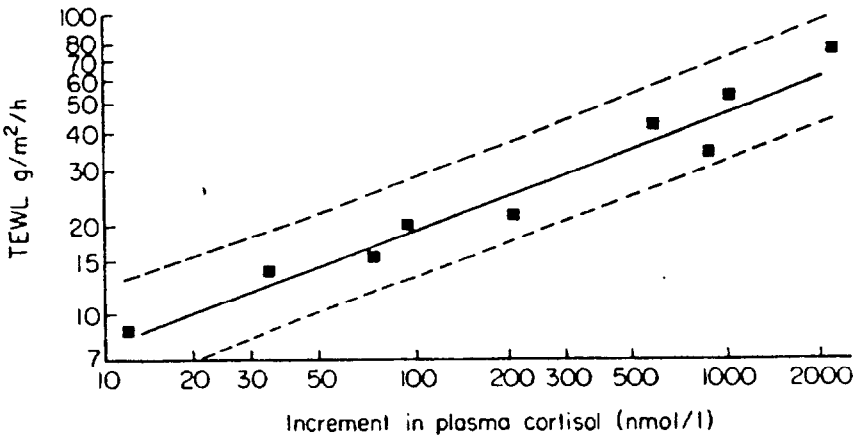
Linear correlation between TEWL (measured after 1 h) and the fraction of the dose of tritiated water absorbed (in 4 h) after various physical injuries applied to excised human skin.

Punnagoda et al. [15] summarized the individual-related variables to transepidermal water loss, and noted that the intra-individual variation of baseline TEWL values is considerably less than the inter-individual variation.

Discussion

Human skin has barrier properties designed through evolution to protect the inner body from the environment. This barrier property is not absolute, and chemicals on the skin can pass into and through the skin by passive diffusion. These same barrier properties are also leaky to the body's water content and water escapes, through the skin, also by passive diffusion. This two way passive travel through the same membrane suggests a correlation between percutaneous absorption and transepidermal water loss, especially in the same individual. Science involves seeking a truth amongst a multitude of variables.

Figure 3



Relation between TEWL and the increment in plasma cortisol in the percutaneous absorption test, in nine patients with widespread dermatitis. Log_{10} scales have been used to normalize the skewed distributions of the two variables. 95% confidence limits are given. The regression line is: $\log_{10}$ TEWL = 0·39 $\log_{10}$ plasma cortisol + 0·51. Spearman's rank correlation coefficient r_s is 0·991 ($P<0·001$; 95% confidence limits for r_s 0·955–0·998).

It is sometimes possible, especially with hydrophilic compounds, to utilize in vitro data to mimic and seek to predict in vivo experience. In vitro diffusion systems have been used in an attempt to determine whether there is a correlation between transepidermal water loss and percutaneous absorption, with mixed results. Nangra et al. [13] demonstrated linear correlation between tritiated water absorbed and TEWL for various sodium lauryl sulfate treatments and for various physical injuries applied to the excised skin (figure 4). Chilcott et al. [14] on the other hand found no correlation between basal transepidermal water loss rates and the permeability of human epidermal membranes to $^3H_20$ ($p = 0.72$) or sulfur mustard ($p = 0.74$). Similarly, no correlation was seen between transepidermal water loss rates and the $^3H_20$ permeability of full-thickness pig skin ($p = 0.68$). There

Despite the many variables in both percutaneous absorption and transepidermal water loss, some statistically positive correlations have been determined between the two. This is not absolute, and negative reports do exist. TEWL also has the added variable of active water exchange for heat dissipation. Because there is significant inter-subject variability in TEWL, the correlation provides evidence confirming the inter-subject variability of percutaneous absorption.

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